The Woodchuck Model of Hepadnavirus Infection and Disease

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The Eastern woodchuck (*Marmota monax*) harbors a DNA virus (Woodchuck Hepatitis Virus, WHV) that is similar in structure, genetic organization, and replication life cycle to the human HBV. Like HBV, WHV infects the liver and can cause acute and chronic hepatitis. The infection of neonatal woodchucks born in the laboratory with standardized inocula produces a high rate of chronic WHV carriers that are useful for controlled investigations in a reasonable time frame. Woodchucks chronically infected with WHV develop progressively severe hepatitis, which presents as lesions that are highly similar to those associated with HBV infection. WHV has been shown experimentally to cause hepatocellular carcinoma (HCC), supporting conclusions based on epidemiological and molecular virologic studies that HBV is an important etiological factor in human hepatocarcinogenesis. Median HCC-free survival in WHV carriers is 24 months, with a median life expectancy of 30-32 months; life expectancy of uninfected animals in captivity is approximately 7 years. Chronic WHV-carrier woodchucks have become a valuable animal model for the preclinical evaluation of antiviral therapy for HBV infection, providing useful pharmacokinetic and pharmacodynamic results in a relevant animal disease model that have been predictive for numerous antiviral agents that have progressed to clinical trials, including drugs now licensed for the treatment of HBV infection (lamivudine, adefovir dipovoxil, entecavir), and agents in late-stage clinical trials (clevudine, emtricitabine, telbivudine, tenofovir disoproxil fumarate). The pattern of toxicity and hepatic injury observed in woodchucks treated with chemotherapeutic agents is remarkably similar to that observed in humans that were treated with the same drugs, suggesting the woodchuck has significant utility for the preclinical assessment of antiviral drug toxicity. The woodchuck/WHV model continues to serve as an important, predictive model for innovative forms of therapy of chronic hepatitis B, such as the use of nucleosides in combination with therapeutic vaccination as an immune response modifier. The delay or prevention of HCC using antiviral therapy has been demonstrated in the woodchuck, establishing a “proof of principal” that has recently begun to be observed in man following long-term therapy. The woodchuck model has also been used in vaccination studies, including early demonstrations of the prevention of chronicity and HCC in a controlled setting. In recent years, the woodchuck has served as a fundamental model of “occult” hepatitis B infection. The model continues to be available for fundamental investigations of the viral and molecular mechanisms responsible for hepatocarcinogenesis and future development of innovative methods for therapy of human HCC.